Outcome of Embolism in the Presence or Absence of Genetic and Acquired Risk Factors and its relationship with Pulmonary Artery Pressure after Six Months of Treatment

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Abstract: Thrombophilia greatly increases the risk of pulmonary thrombosis. Many genetic and acquired factors are involved in thromboembolism. From the genetic factors we can mention two autosomal genetic mutations, such as mutation of factor V Leiden and prothrombin gene mutation. Materials and Methods: In a descriptive-analytic study, 60 patients with thromboembolism who had inclusion criteria were selected and divided into two groups of genetic and acquired thromboembolism risk factors (groups A and B with 30 patients in each group). All patients in both groups were investigated in terms of outcome of embolism in relation with the presence or absence of genetic or acquired risk factors and its relationship with pulmonary artery pressure at the beginning of study and six months after the treatment. In total, 31 patients (56.4%) were male and 24 patients (43.6%) were male. The mean age of the study population was 44.4 ± 14 years (the age range was from 23 to 75 years old). The relationship of stability of blood clots in the pulmonary artery and genetic risk factors, after six months of treatment, was statistically significant (P=0.03). However, the relationship between pulmonary artery pressure and genetic and acquired risk factors was not significant (P=0.24). According to the presence of significant relationship between genetic risk factors and outcome of pulmonary embolism, by adopting specific prevention and cure measures (such as genetic engineering), we can stop many pulmonary complications and mortality which helps patients and the healthcare system.

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1. Introduction

As we know, acquired and genetic factors are involved in susceptibility to venous thromboembolism. Predisposition to thrombosis (thrombophilia) greatly increases the risk of pulmonary thrombosis. Two prevalent genetic mutations autosomal that can lead to pulmonary thromboembolism are mutation of factor V Leiden and prothrombin gene mutation (Pengo V, Lensing AW, Prins MH.; 2004).

The most appropriate test to confirm the diagnosis of pulmonary thromboembolism is elective pulmonary angiography which can detect the emboli as small as 1-2 millimeter. Nowadays, pulmonary diagnostic angiography is replaced with chest CT scan with contrast medium. Today, in the places where there are facilities of modern CT scan with contrast medium, angiographic is used only when it is required to perform interventions like thrombolysis or embolectomy with the catheter (Auger WR, Kim NH, Kerr KM.; 2007).

In several studies, the sensitivity and specificity of CT Pulmonary angiography for the diagnosis of pulmonary thromboembolism are 93% and 98%, respectively which is equal to the value of pulmonary angiography (the gold standard of diagnosis). However, it is less invasive than angiography, is faster, has fewer complications, and is performed in a breathing stop by the patient (Meignan M, Rosse J, Gauthier H.; 2000). Pulmonary CT angiography is used to for diagnosis of main pulmonary artery stenosis, changes in the size of lobar vessels and segmenter, determining the intensity of pulmonary stenosis, and right ventricle and atrium enlargement (Bonderman D, Jakowitsch J, Adlbrecht C.; 2005 and Qassem A, Snow V, Barry P.; 2007). Pulmonary CT angiography does not provide information on the hemodynamic and pulmonary artery pressure (Paul G, Charles S.; 2000). Information about the size and rate of clot resolution in pulmonary embolism are contradictory. Fragmentation, clot fibrinolysis by the physiology of the body, and recanalization are among the common clot removal mechanisms. The two latter mechanisms will initiate weeks after the forming of clots and have no role in the acute phase (Paul G, Charles S.; 2000).

In a study by Salah D. Qanadli and colleagues (2000), they investigated 54 patients, including 35 males and 19 females with a mean age of 56 years and calculated the percent index of pulmonary artery

thrombosis in patients with pulmonary embolism through CT angiography as following method. They divided each of the right and left pulmonary arteries into 10 segments (three branches for the upper lobes, two branches for middle lobes, and five branches for the lower lobes). Existence of embolism in each branch has 1 point. The embolism in more proximal branches gives points equal to the branches at the segments. To determine the extent of obstruction of the arteries, each partial obstruction or the existence of partial perfusion gives 1 point and each complete occlusion or the lack of perfusion gives 2 points.

The isolated embolism in sub-segmental branches is considered as the partial occlusion of segmental vessel (one point). Therefore, the maximum score for complete occlusion is 40 and the percent of pulmonary artery occlusion is calculated from the following equation (Lang I, Kerr K.; 2006):

Number of segmental branch with embolism × extent of stenosis=calculated score for patient

100 × (40 / points calculated for patient) = percentage of pulmonary artery occlusion

The percentage of calculated pulmonary artery stenosis by the above method is comparable with the percentage of calculated pulmonary artery stenosis in pulmonary angiography (as the golden standard) and there significant relationship between them (Lang I, Kerr K.; 2006).

Given that, there are few studies in this field, worldwide, and moreover, due to the lack of such study in our country, we have decided to investigate the outcome of emboli in relation with the presence or absence of genetic or acquired risk factors and its relationship with pulmonary artery pressure after six months of treatment of the patients.

2. Material and Methods

In a descriptive-analytic study, 60 patients with thromboembolism who had inclusion criteria were selected and divided into two groups of genetic and acquired thromboembolism risk factors (groups A and B with 30 patients in each group). The total study duration was 8 months from November 1389 to June 1390 to gather preliminary data and analysis of the data.

For each of the patients, pulmonary CT angiography was conducted via multi-slice CT 64 (Siemence (Somatom Sensation 64)) CT scan equipment using Ultavis 370mg (Schering BG) contrast medium. This contrast medium is a nonionic water-soluble material containing 370 mg/Lit of iodine (60-70^{cc}). According to the situations of patients, Test-bolus or Bolus Trachiking methods were used for the interval between injections of contrast medium and scanning. The scanning was conducted in supine position from neck to the diaphragm. The thicknesses of slices were 0.6 mm and after scanning, the data were reconstructed in a workstation with 1 mm of thickness and 0.5 mm of distance between slices. The data were examined using MPR and MIP methods as well as three-dimensional reconstruction through VRT method when needed. After the diagnosis of acute pulmonary thromboembolism, the patients were entered to study. All patients of both groups were reinvestigated after six months from treatment in terms of the outcome of embolism in relation with the presence or absence of genetic or acquired risk factors and their relationships with pulmonary artery pressure.

2.1. Exclusion criteria

1. Heart diseases such as valvular heart diseases, which can lead to increased pulmonary arterial pressure.
2. Congestive heart failure and congenital heart diseases
3. Lung diseases such as obstructive pulmonary diseases (asthma, COPD,…)
4. Interstitial lung diseases
5. Intra-pulmonary shunts
6. Smoking

2.2. Statistical Analysis

The obtained results are reported in terms of Mean ± SD and frequency-percentage. The statistical software used was SPSS Version 16. In order to compare quantitative and qualitative variables, student T-test and Qui-square methods were used, respectively, as well as Paired T-test when needed. In all of studied cases, the results were considered as statistically significant if $P < 0.05$.

3. Results

Five patients of group A were excluded due to lack of access and follow up visit in order to perform secondary CT angiography after six months, thus, the information of 25 patients of intervention group were analyzed and compared with control group.

Age and Sex

In total, 31 patients (56.4%) were male and 24 patients (43.6%) were female who were divided into two groups A (18 males and 7 females) and B (13 males and 17 females). The mean age of the study population was 44.4±14 years from 23 to 75 years old. The mean age of A and B groups were 42.9±14.2 (23-66 years old) and 45.6±14 (28-75 years old), respectively.

Family history of PTE

In group A, the family history of PTE was positive for 3 patients (12%) and negative for 22 patients (88%). In group B, the family history of PTE was positive for 4 patients (13.3%) and negative for 26 patients (86.7%). In this respect, the difference between the two groups was not statistically

significant (P=0.60), thus, there was no bias in the results.

Acquired risk factors of PTE

The acquired risk factors of pulmonary thromboembolism in patients of group are presented in the following table in terms of their prevalence.

Table 1: Comparison of frequency of acquired risk factors

Etiology	The group acquired risk factor N = 30 patients
Surgery	12 patients (40%)
Severe trauma	8 patients (26.6%)
Prolonged immobility	4 patients (13.4%)
Cancer	3 patients (10%)
Severe Obesity	3 patients (10%)

3.1. Comparison of pulmonary artery stenosis at the beginning of the study

As previously mentioned, the extent of pulmonary artery stenosis is calculated, based on the presented formula, once at beginning of the study and once after six months of treatment as the following.

The pulmonary artery stenosis in patients with genetic risk factors (group A) was 34.2 ± 26.5 percent which was within the range of 1.5-85 percent. Moreover, in patients with acquired risk factors (group B) it was 33.6 ± 25.4 percent which was within the range of 3-85 percent. The differences between the two groups at the beginning and after six months, in terms of pulmonary artery stenosis, was not statistically significant (P=0.93) and the groups were identical.

3.2. Comparison of residual pulmonary artery stenosis at the beginning of the study

Six months after treatment, the initial diagnostic procedure was performed for all patients in which, 4 patients (16%) of group A (Genetic risk factors) and still had PTE. However, none of the patients of group B (acquired risk factors) have evidences of PTE. For the negative cases, the clot was completely dissolved via fibrinolysis process and there was no evidence of pulmonary embolism in the CT angiography. The difference between the two groups, in terms of persistence of PTE after six months of treatment was statistically significant (P=0.03). In other words, the relationship between durability of blood clots, six months after treatment, and genetic risk factors is enhanced.

3.3. Comparison of pulmonary hypertension (PHTN)

Six months after the treatment, the pulmonary arterial hypertensions in patients of both groups were compared. As we know, PHTN is the pulmonary artery pressure above 20 mm Hg. The increase of pulmonary arterial pressure was observed in 7 (28%) and 5 (16.7%) patients of groups A and B, respectively. The difference between the two groups, in terms of increased pulmonary arterial pressure after six months of treatment, was not statistically significant (P=0.24). The number of dialysis sessions per week in patients of A and B groups were 2.7 ± 0.4 and 2.8 ± 0.4 sessions, respectively. The difference between the two groups, in terms of the number of dialysis sessions per week, was not statistically significant (P=0.72).

4. Discussions

As mentioned above, the most appropriate test to confirm the diagnosis of pulmonary thromboembolism is elective pulmonary angiography which can detect the emboli as small as 1-2 millimeter. Nowadays, pulmonary diagnostic angiography is replaced with chest CT scan with contrast medium. Today, in the places where there are facilities of modern CT scan with contrast medium, angiographic is used only when it is required to perform interventions like thrombolysis or embolectomy with the catheter (Auger WR, Kim NH, Kerr KM.; 2007).

Qanadli and colleagues (2001), in a similar study, investigated special indices in order to determine the pulmonary artery occlusion in patients with pulmonary thromboembolism. Their results showed that, the extent of pulmonary artery occlusion in PTE has close relationship with the outcome of embolism in pulmonary branches (Qanadli S, Hajjam M, Baron A.; 2001). Their study was conducted on 158 patients with PTE in which, the levels of pulmonary artery stenosis, at first, in patients with genetic risk factors and the other group were 43 ± 25 percent and 36.6 ± 10.4 percent, respectively, where the difference was statistically significant (P=0.0001) (Qanadli S, Hajjam M, Baron A.; 2001).

In our study, unlike the study of Qanadli, the pulmonary artery stenosis rate in patients with genetic risk factors (group A) was 34.2 ± 26.5 percent, which was within the range of 85-1.5 percent. In addition, in patients with acquired risk factors (group B) it was 33.6 ± 25.4 percent, which was within the range of 3-85 percent. The difference between the two groups, in terms of pulmonary artery stenosis at the beginning, was not statistically significant (P=0.93).

In the work of Qanadli and colleagues, the increase of mean pulmonary artery pressure (PHTN) was only observed in 25 patients (15.8%) and its relationship with outcome of embolism and the early stenosis was not statistically significant (P=0.08) (Qanadli S, Hajjam M, Baron A.; 2001). In this work, similar to Qanadli, in the case of patients of groups A and B, an increase in pulmonary arterial pressure were observed in 7 patients (28%) and in 5 patients (16.7

percent), respectively. Similarly in our work, the difference between the two groups, in terms of increased pulmonary arterial pressure after six months of treatment, was not statistically significant (P=0.24).

In another similar study in Austria, Lang and colleagues (2006) have investigated the genetic risk factors of pulmonary thromboembolism i.e. the genetic mutations involved in PTE (8). In this study, the most common mutations associated with PTE were Factor V and Factor II mutations. In their study, from 100 studied patients, 14 cases (14%) had a positive family history of pulmonary thromboembolism (Andrew S, Pezzullo J, Hou D, and Smith M.; 2004). Similarly in our study, 3 (12%) and 4 (13.3%) of patients had positive family history of pulmonary thromboembolism. In our study, this difference between the two groups was not statistically significant (P=0.60). In our study, a nearly complete gene mutations associated with pulmonary thromboembolism (including 13 gene mutations) was studied for the first time.

As mentioned, in the laboratory setting, the genes, in terms of expression, were categorized as zero for being negative gene, 1 for being heterozygous, and 2 for being homozygous. We also studied patients in terms of the expression of various genes and found that, a patient at the same time, in terms of genetic expression, was negative (the lack of expression) heterozygous and homozygous. In this work, similar to Lang and colleagues, the most common mutations were in the factor V genes, Methylene Hydrofolate reductase (MTHFR 1298 A/C), ACE mutation, and tissue plasminogen activator (TPA intron 8 D/I).

Andrew and colleagues, in a descriptive-analytic have showed that, the measured stenosis by CT Angiography is an important prognostic factor to predict the outcome of pulmonary embolism (Masotti L, Righini M, Ray P.; 2009). In the present work, in general, the primary stenosis was 22 ± 23.2 percent which were in the range of 3-80 percent. The ratio of female to male patients, in this study, was almost 2 to 1, and the mean age of patients was 61 ± 18.4 years.

In the study of Andrew and colleagues, six months after the treatment, CT Angiography diagnostic procedure was performed on patients, in which in 2 cases, embolism was completely destroyed and the evidences of PTE was observable. In their study, the relationship between the outcome of embolism with initial pulmonary artery stenosis was statistically significant (P=0.002) (Masotti L, Righini M, Ray P.; 2009).

Similar to the work of Andrew, six months after treatment, we performed primary diagnostic procedure on all patients in the two groups, of which 4 (16%) of the patients of group A (Genetic risk factors) still had PTE. However, none of the patients of group B (acquired risk factors) have evidence of PTE. In the negative cases, the clot was completely dissolved through fibrinolysis process and there are no evidences of pulmonary embolism in the second CT angiography. The difference between the two groups, in terms of persistence of PTE after six months after treatment, was statistically significant (P=0.03).

Similar to our study, Masotti et al. investigated the pulmonary artery stenosis rates and the relationship between the outcome of pulmonary embolism and genetic and acquired risk factors. In this study, the relationship between outcome of embolism and the presence of genetic risk factors was significant (P=0.01).

In the study of Masotti and colleagues, among the underlying acquired risk factors for PTE, the frequency of surgery and prolonged recovery risk factors were more than others. However, in our study, in the group of acquired risk factors, surgery (40%) and trauma (26.6%), respectively, were the greatest risk factors for pulmonary thromboembolism.

Given the significant relationship between genetic risk factors and outcome of pulmonary embolism, by adopting specific prevention and cure measures (such as genetic engineering), we cans top many pulmonary complications and mortality which helps patients and the healthcare systems.

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